ADVANCED MEDICAL OPTICS

RECORD OF INVENTION

Date: 10/15/02 **ROI No.** MP/RW/RG-02-78

Surgical	CLCP
IOLs (IO):	**Multi-Purpose Sol'ns (MP):** X
Inserters (IN):	**Rewetters/In-the-Eye Cleaners (RW):** X
Phaco. Equip. (PH):	**RGP Sol'ns (RG):** X
Refractive (RE):	**Hydrogen Peroxide Sys. (HY):**

Other (OT):

1. **PROPOSED TITLE OF INVENTION:**

Self Emulsifying Ophthalmic Emulsion Compositions, Methods of Use and Preparation

2. **GENERAL DESCRIPTION:** (If new device, include drawings and list of required components or features and functions performed, if chemical compound – formula of generic concept, sample preparation from known starting materials. If new composition or use – ingredients, inherent/essential properties and preparation. If chemical process – critical components and operation. Pinpoint novel features. Point out use or advantage of invention in detail. Indicate specific compounds of interest by name and AMO Compound Number with test results. Attach additional pages or diagrams as necessary.)

The present invention relates to compositions and methods for eye and contact lens care. More particularly, the invention relates to ophthalmic compositions which are self-emulsifying, oil-in-water emulsions.

Typical preparation of oil-in-water emulsions has involved dissolving water-soluble components in an aqueous phase and dissolving oil-soluble components in an oil phase. The oil phase is vigorously dispersion mixed into the aqueous phase at several thousand r.p.m. for minutes to several hours. Manufacturing procedures employing such methods involve significant investment in capital equipment, are time consuming and cannot be easily scaled-up to larger batch sizes. Also, it is generally difficult to stabilize oil-in-water emulsions prepared by these types of methodologies for the commercially desired shelf-life of two-years without incorporating viscosity builders. However, high viscosity is often undesireable for ophthalmic solutions and almost universally unacceptable for contact lens care solutions. A two-year shelf-life can sometimes be achieved if the emulsions are stored refrigerated, however, the use of refrigeration causes limitations for commercial distribution of the product.

Sterilization is essential for many oil-in-water emulsions, which readily support the growth of bacteria, the latter which give rise to contamination of the composition. A problem encountered with emulsions prepared by standard methods is that they are not easily sterilized using filtration techniques. Filter sterilization for ophthalmic

compositions which comprise oil-in-water emulsions is preferred to heat sterilization because of problems associated with heat sterilization such as manufacturing complexity and cost. Also, precipitation and/or inactivation of composition components may occur in sterilization procedures where heat is used.

Surfactants are utilized as emulsifiers in oil-in-water emulsions. Oil-in-water emulsions prepared via conventional methods generally require high surfactant to oil ratios. Oil-in-water emulsions with a low surfactant to oil ratio generally produce a higher degree of ocular comfort than those with a high surfactant to oil ratio. Ocular comfort is of critical importance for commercial success in products such as eye drops and contact lens multipurpose solutions.

Additionally, oil-in-water emulsions prepared via methods other than those described in the invention generally require two or more surfactants, resulting in high surfactant to oil ratios and problems with achieving low toxicity, very safe compositions along with increasing complexity of the compositions.

In view of these and other limitations to oil-in-water emulsions prepared by standard techniques, it would be advantageous to have oil-in-water emulsions which are easily prepared and sterilized, are storage stable, have a low surfactant to oil ratio for applications requiring high comfort, and employ fewer surfactants to achieve emulsification.

Self-emulsifying oil-in-water ophthalmic emulsion compositions, methods of use and preparation have been discovered which achieve the aforementioned advantages. These emulsions employ molecular self-assembly methods to generate macromolecular oil droplet structures at the nanometer scale, and thus represent an example of nanotechnology. The emulsions are easily prepared via molecular self-assembly in milli-seconds to minutes, can be filter sterilized, are storage-stable, and employ only one or two surfactant emulsifiers to achieve low surfactant to oil ratios and non-toxic, comfortable solutions.

Topical ophthalmic applications for the emulsions of the present invention include eye drops for dry eye treatment, compositions for delivery of drugs, and contact lens care solutions. Contact lens care solution applications include multipurpose cleaning, rinsing, disinfecting and storage solutions, rewetting, in-the-eye cleaning and other solutions.

The integration of oil-in-water emulsions into eye drops for dry eye treatment, contact lens rewetting and multipurpose solutions adds the additional utility of prevention of dry eye and contact lens water loss by providing an oil layer at the air-tear interface or additionally at the contact lens-tear interface when a contact lens is present. This oil layer acts to prevent dry eye or contact lens water loss by retarding water evaporation and thus loss. The oil layer on the surface of a contact lens can also provide a long-lasting lubrication layer, especially for rigid gas permeable contact lenses. The oil layer on the surface of a contact lens can also inhibit contact lens protein deposition.

The emulsions of the present invention include an oily component which may include an oil or oils, a surfactant component which includes one or two surfactants, and an aqueous component which includes an aqueous phase.

The oil may be polar or non-polar in nature and naturally or synthetic derived. The oil may be a mono, di or triglyceride of fatty acids or mixtures of glycerides, such as Castor oil, Coconut oil, Cod-liver oil, Corn oil, Olive oil, Peanut oil, Safflower oil, Soybean oil and Sunflower oil. The oil may also be comprised of straight chain monoethylene acids and alcohols in the form of esters, such as Jojoba and Sperm Whale oil. The oil may also be comprised of liquid hydrocarbons from petroleum, such as mineral oil. The oil may be synthetic, such as silicone oil. The oil also may be comprised of water insoluble non-volatile liquid organic compounds, e.g., a racemic mixture of Vitamin E acetate isomers. Mixtures of the above oil types may also be used.

Oils which are natural, safe, have prior ophthalmic or other pharmaceutical use, have little color, do not easily discolor upon aging, easily form spread films and lubricate surfaces without tackiness are preferred. Castor oil is a preferred oil.

Surfactants may be non-ionic, cationic, anionic or amphoteric in nature. Non-ionic surfactants are preferred, due to their higher compatibility with ocular tissues and contact lenses. One or two surfactants are selected to match a particular oil or oils which respect to the ability of the surfactant or surfactants to form a self-emulsifying oil-in-water emulsion. A single surfactant must meet two chemical structural requirements to achieve self emulsification: (1) the surfactant must have an affinity for the selected oil or oils based upon non-covalent bonding interactions between the hydrophobic structures of the surfactant and the oil(s) such that self emulsification can be achieved when requirement (2) is simultaneously met; and (2) the surfactant must have a chemical structure which is wedge or pie section-shaped, with the larger end of the wedge structure closer to the hydrophilic part of the surfactant structure. This wedge-shape is believed to induce spherical oil droplet curvature at the aqueous-oil interface due to the molecular self-assembly of adjacent surfactant wedges at the aqueous-oil interface. Thus, the geometry of the wedge-shaped surfactant molecules is intimately related to the oil droplet curvature. Steric repulsion in the aqueous phase between the hydrophilic parts of adjacent surfactant molecules facilitates this. Preferably, these hydrophilic parts consist of polyethyleneoxide chains of an appropriate length. Preferably, the polyethyleneoxide chains are from 7-20 ethyleneoxide units in length. When the aforementioned two structural requirements are met for a surfactant and oil(s) pair(s), an empirical test of self emulsification is conducted while varying the concentrations of the surfactant and oil components. The empirical test of self emulsification is conducted employing the methods of preparing self emulsifying emulsions described herein. An emulsion is considered to be acceptable when it appears to be homogeneous when observed by eye, without any appearance of flocculation, cream or phase separation between the aqueous and oil phase and also when the oil droplet size distribution of the emulsion meets particular product criteria for emulsion stability. A preferred example of a single surfactant and oil pair is the surfactant Lumulse GRH-40 and Castor oil.

Lumulse GRH-40 is a 40 mole ethoxlate of hydrogenated Castor oil. Lumulse GRH-40 is produced through the catalytic hydrogenation of Castor oil at the 9-carbon positions of the three ricinoleic acid glycerol ester chains, followed by ethoxylation of the three 12-hydroxy groups of the resulting 12-hydroxystearic acid glycerol esters with about 13 ethoxy groups each. It is believed that self emulsification of Castor oil with Lumulse GRH-40 occurs due to the folding of the 6-carbon alkyl chain distal to the ethoxylated 12-hydroxy group inwards against the remaining 10-carbon alkyl segment of the stearate ester group to form a wedge-shaped hydrophobic part of the molecule, the orientation of

the ethoxy groups outwards into the water phase, the orientation of the wedge-shaped hydrophobic part of the molecule into the Castor oil phase (narrow part of the wedge facing inwards away from the aqueous phase) and the affinity of the wedge-shaped hydrophobic part of the molecule for Castor oil.

The optimal amount of Lumulse GRH-40 to use in conjunction with Castor oil is about 0.8 w/w% Lumulse GRH-40 for 1.0 w/w% Castor oil. Higher or lower amounts in conjunction with Castor oil can be used, however, depending upon the desired properties of the final emulsion.

Lumulse GRH-40 can be combined with other surfactants such as Polysorbate-80 (Tween-80, polyoxyethylene (20) sorbitan mono-oleate) to create self-emulsifying emulsions comprised of two surfactants. In such compositions, self emulsification is believed to be driven principally by the Lumulse GRH-40 and not interfered by the Polysorbate-80 due to the similar chemical structures of the hydrophobic chains of Polysorbate-80 (oleic acid ester chains) and those of Castor oil (12-hydroxyoleic acid ester chains) and Lumulse GRH-40 (stearic acid ester chains).

Two surfactants may also be selected to match a particular oil or oils which respect to the ability of the surfactants to form a self-emulsifying oil-in-water emulsion. Both surfactants must each meet two chemical structural requirements to achieve self emulsification: (1) each surfactant must have an affinity for the selected oil or oils based upon non-covalent bonding interactions between the hydrophobic structures of the surfactant and the oil(s) such that self emulsification can be achieved when requirement (2) is simultaneously met; and (2) the surfactant pair must be able to form a chemical structure which is wedge or pie section-shaped, with the larger end of the wedge structure closer to the hydrophilic parts of the surfactant structures. A preferred example of a surfactant pair which is compatible with an oil is the surfactant raw material Cremophor RH-40, which is comprised of two surfactants, and Castor oil. Cremophor RH-40 from the BASF Corporation is comprised 75-78% of two surfactants: the trihydroxystearate ester of polyethoxylated glycerol and the hydroxystearate (bis) ester of mixed polyethylene glycols, along with 22-25 % free polyethylene glycols. The Cremophor RH-40 raw material thus has two surfactants which are structurally related to each other and to Castor oil. It is believed that the combination of a surfactant with three ester chains with a surfactant with two ester chains, wherein all of the chains have an affinity for each other, allows the formation of a wedge-shaped structure in the presence of Castor oil wherein the two surfactants alternate at the oil droplet interface. Cremophor RH-60 is an example of another surfactant raw material comprised of two surfactants. Cremophor RH-60 is identical to Cremophor RH-40, with the exception that there is a higher derivatization with polyethyleneglycol with RH-60 than with RH-40.

Additional surfactant may be added which may or may not participate in emulsion formation.

The preparation of the oil-in-water emulsions of the present invention is generally as follows: the two phases (oil and water) are separately heated to an appropriate temperature. This temperature is the same in both cases, generally a few degrees to 5 to 10 degrees above the melting point of the highest melting ingredients in the case of a solid or semi-solid oil or emulsifying agents in the oil phase. Where the oil phase is liquid at room temperature, a suitable temperature is determined by routine experimentation

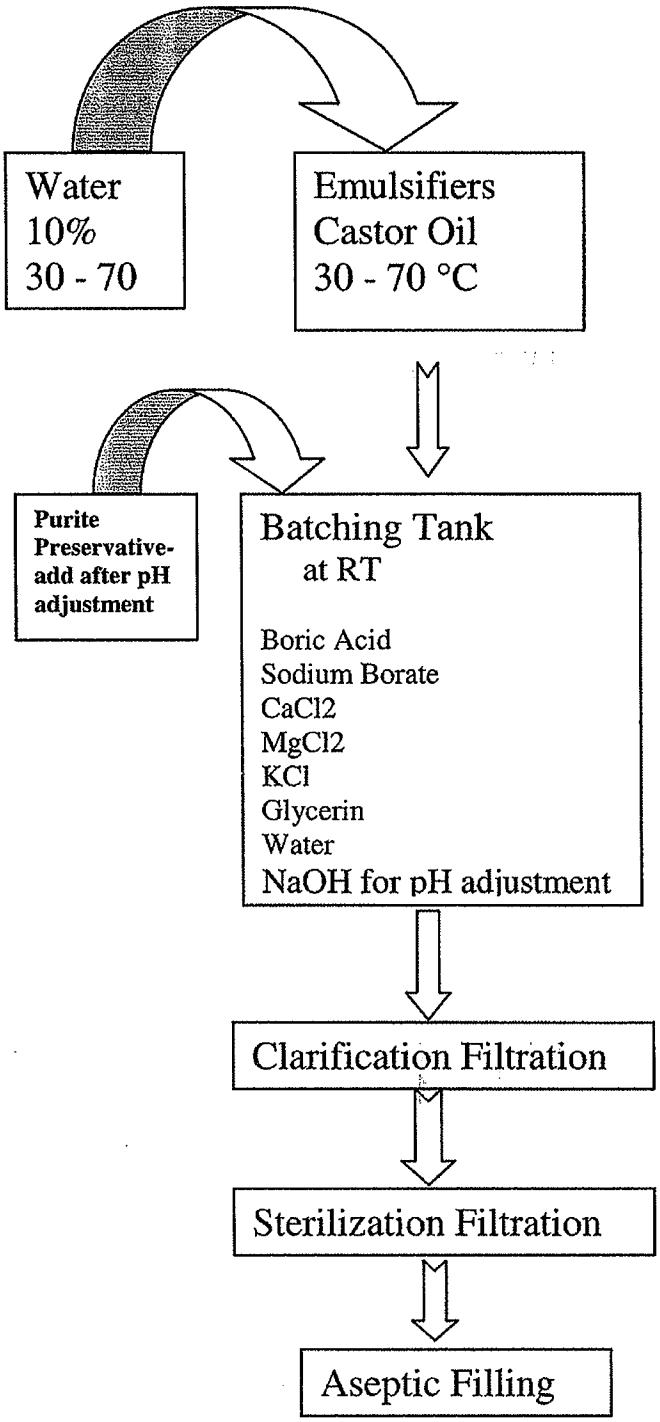
with the melting point of the highest melting ingredients in the aqueous phase. In cases wherein all components of either the oil or water phase are soluble in their respective phase at room temperature, no heating may be necessary. Non-emulsifying agents which are water soluble components are dissolved in the aqueous (water) phase and oil-soluble components including the emulsifying agents are dissolved in the oil phase. To create an oil-in-water emulsion, the final oil phase is gently mixed into either an intermediate, preferably de-ionized water phase, or the final aqueous phase to create a suitable dispersion and the product is allowed to cool with or without stirring. In the case wherein the final oil phase is first gently mixed into an intermediate water phase, this emulsion concentrate is thereafter mixed in the appropriate ratio with the final aqueous phase. In such cases, the emulsion concentrate and the final aqueous phase need not be at the same temperature or heated above room temperature, as the emulsion has already been formed at this point.

Semisolids may form in the process of self-emulsification if the amount of ethyleneoxide units in one emulsifier is too large. Gentle mixing may then be required until the hydrated emulsifiers are fully dissolved to form the emulsion.

The oil-in-water emulsions of the present invention can be sterilized after preparation using autoclave steam sterilization or can be sterile filtered using a 0.22 micron sterile filter. Sterilization employing a sterilization filter can be used when the emulsion droplet (or globule or particle) size and characteristics allows this. The droplet size distribution of the emulsion need not be entirely below the particle size cutoff of the 0.22 micron sterile filtration membrane to be sterile-filtratable. In cases wherein the droplet size distribution of the emulsion is above the particle size cutoff of the 0.22 micron sterile filtration membrane, the emulsion needs to be able to deform or acceptably change while passing through the filtration membrane and then reform after passing through. This property is easily determined by routine testing of emulsion droplet size distributions and percent of total oil in the compositions before and after filtration. Alternatively, a loss of a small amount of larger droplet-sized material may be acceptable.

The emulsions of the present invention are generally non-aseptically filtered through a clarification filter before sterile filtration or aseptically after autoclave steam sterilization. Thereafter, the emulsions are aseptically filled into appropriate containers.

The following example illustrates the preparation of an emulsion of the present invention.


Water
10%
30 - 70
Emulsifiers
Castor Oil
30 - 70 °C
Purite
Preservative-
add after pH
adjustment
Batching Tank
at RT
Boric Acid
Sodium Borate
CaCl2
MgCl2
KCl
Glycerin
Water
NaOH for pH adjustment
Clarification Filtration
Sterilization Filtration
Aseptic Filling

The following examples can be used either as eye drops for dry eye treatment or as contact lens rewetters:

	Example 1	Example 2
Ingredient	**% w/w**	**% w/w**
Cremophor RH-60	1.75	
Cremophor RH-40		1.5
Castor Oil	1.25	1.25
Balanced Electrolytes	0.397	
Glycerin		1.00
Pemulen TR-2		0.10
Boric Acid	0.60	0.60
Purite® (2.15 w/v%)	0.37	0.37
Sodium Hydroxide To adjust pH to about 7.4		
Purified Water	q.s. 100	q.s. 100

	Example 3	Example 4	Example 5	Example 6
Ingredient	**% w/w**	**% w/w**	**% w/w**	**% w/w**
Lumulse GRH-40	1	1.2	1	1
Castor Oil	1.35	1.5	1.25	1.25
Boric Acid	0.6	0.6	0.6	0.6
Sodium Borate 10H2O	0.035	0.035		
CaCl2.2H2O	0.006	0.016		
MgCl2.6H2O	0.006	0.006		
KCl	0.14	0.14		
NaCl	0.25	0.25		
Glycerin			1	1
HPMC		0.1	0.1	
Pemulen TR-2				0.10
Purite® (2.15 w/v%)	0.37	0.37	0.37	0.37
pH	7.621	7.321	7.3	
Viscosity (cps)		40.9	41.3	
Osmolality (mOsm)	230	247	230	
Particle Mean Size (um)	0.14	0.14	0.14	
99% Cumulative Size (um)	0.263	0.19	0.27	

	Example 7	Example 8
Ingredient	% w/w	% w/w
Lumulse GR-40	1.5	1.5
Castor Oil	1.25	1.25
Boric Acid	0.6	0.6
Sodium Borate 10H2O	0.035	0.035
CaCl2.2H2O	0.006	0.006
MgCl2.6H2O	0.006	0.006
KCl	0.14	0.14
Glycerin	1	1
HPMC (F4M)	0.7	
Purite® (2.15 w/v%)	0.37	0.37
pH	7.5	7.3
Viscosity (cps)	64.8	
Osmolality (mOsm)	271	
Particle Mean Size (um)	0.33	
99% Cumulative Size (um)	0.66	

	Example 9	Example 10	Example 11	Example 12
Ingredient	% w/w	% w/w	% w/w	% w/w
GRH-40	1	3.2	0.4	0.75
Castor Oil	1.25	4	1	1.25
Tween-80			0.4	0.25
Boric Acid	0.6	0.6	0.6	0.6
Sodium Borate 10H2O	0.035	0.035	0.035	0.035
CaCl2.2H2O	0.006	0.016	0.006	0.006
MgCl2.6H2O	0.006	0.006	0.006	0.006
KCl	0.14	0.14	0.14	0.14
NaCl				0.42
Glycerin	1	1	1	
Purite® (2.15 w/v%)	0.37	0.37	0.37	0.37
pH	7.31	7.38	7.37	7.39
Viscosity (cps)				
Osmolality (mOsm)	285	288		285
Particle Mean Size (um)	0.125	0.136	0.16	0.1375
99% Cumulative Size (um)	0.248	0.291	0.31	0.253

Contact lens multipurpose solutions.

	Example 13	Example 14
Ingredient	**% w/w**	**% w/w**
PHMB (ppm)	1.1	1.1
HPMC	0.15	0.15
Propylene Glycol	0.5	0.5
Dibasic Sodium Phosphate·7H2O	0.12	0.12
Monobasic Phosphate·H2O	0.01	0.01
EDTA	0.01	0.01
NaCl	0.55	0.55
KCl	0.14	0.14
Vitamin E Acetate	1.25	1.25
Lumulse GR-40	0.5	
TPGS		1

3. LIST PUBLICATIONS, LITERATURE SEARCHES, PATENTS, ETC. (Attach copies/links as available)

4. PERSONS CORROBORATING INVENTION:

Stanley W. Huth

In consideration of employment and the salary associated therewith, this invention is hereby assigned to Advanced Medical Optics, Inc. together with the rights to any patents associated therewith.

5. INVENTOR(S): (If not a United States citizen, note country)

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Street Address	*City*	*State and Zip Code*	*County of Citizenship*

Signature: _____

APPROVAL FOR SUBMISSION
(Read and Understood)

By: _____
Department Head (Full Name)

Date: 10/22/02

RECEIVED BY AMO LEGAL/ INTELLECTUAL PROPERTY DEPARTMENT

By: _____

Date: 02/10/04